DOCKET NO.: ISPH-0595 PATENT

REMARKS/ARGUMENTS

After entry of this paper, the pending claims are 1, 5, 7, 9-13, and 15. Claims 2, 4, 6, 8, and 14 are canceled, without prejudice. Claims 1 and 11 are amended to specify that the antisense oligonucleotides are 100% complementary to a nucleic acid molecule encoding human apolipoprotein (a) and to incorporate the subject matter of claims 4, 6, and 8. Support for these amendment is found throughout the originally filed specification and claims and on page 9, lines 1-3. No new matter is added by these amendments.

Applicants reserve the right to prosecute the broad language of original claims 1 and 11, as well as any currently or previously deleted subject matter, in a continuation application filed during the pendency of the present application.

35 USC § 102 Rejections

(i) *Claims 1, 2, and 4-15 are rejected under 35 USC § 102(b) over US Patent No. 6,008,344 (Bennett et al.).*

The Examiner asserted that SEQ ID NO: 43 is reverse complementary to nb 457-473 of SEQ ID NO:3 of Applicants' invention, but is not contiguous.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

Claims 2, 4, 6, 8, and 14 are canceled, thereby mooting the outstanding rejection as applied to these claims. Claims 1, 5, 7, 9-13, and 15 are therefore subject to this rejection.

PAGE 6/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26

Bennett discusses antisense compounds for modulating the expression of phospholipase A2 Group IV. The antisense compounds are targeted to nucleic acids encoding phospholipase A2 Group IV.

As the Examiner noted, Bennett teaches an 18 nb nucleic acid sequence (SEQ ID NO: 43) that is reverse complementary, ***but not contiguous***, to nb 457-473 of SEQ ID NO:3 of Applicants' invention. In fact, the Examiner notes that SEQ ID NO: 43 of Bennett contains 2 nb that differ from the nb 457-473 of SEQ ID NO:3 of Applicants' invention. Bennett does not teach or discuss antisense oligonucleotides, specifically compounds 12 to 30 nucleobases in length, targeted and 100% complementary to a nucleic acid molecule encoding human apolipoprotein (a) (apo(A))(SEQ ID NO: 3).

In view thereof, the antisense sequences of Bennett are not targeted to and 100% complementary to the nucleic acid molecule encoding SEQ ID NO: 3, as required by the pending amended claims of Applicants' invention. Since Bennett does not teach the claimed oligonucleotides of Applicants' invention, Bennett cannot teach methods of using the same, such as the method of pending claim 15 of Applicants' invention. Thus, Bennett cannot properly be applied as an anticipation reference.

Reconsideration and withdrawal of this rejection are requested.

PAGE 7/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26

(ii) *Claims 1, 2, 11, 12, and 14 are rejected under 35 USC § 102(b) over US Patent No. 6,080,580 (Baker et al.)*

The Examiner asserted that SEQ ID NO: 43 is reverse complementary to nb 430-445 of SEQ ID NO:3 of Applicants' invention, but contains one mismatch.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

Claims 2 and 14 are canceled, thereby mooting the outstanding rejection as applied to these claims. Further, claim 1 is amended by incorporating the subject matter of claims 4, 6, and 8, which are not subject to this rejection. In view of these amendments, this rejection is moot as applied to claims 1 and 12.

Claim 11 is therefore subject to this rejection.

Baker discusses antisense compounds for inhibiting the expression of human tumor necrosis factor-α (TNF-α) and particularly antisense compounds targeted to nucleic acids encoding TNF-α.

As the Examiner noted, Baker discusses a TNF-α primer having the sequence of SEQ ID NO: 43. This PCR primer is reverse complementary, ***but not contiguous***, to nb 430-445 of SEQ ID NO: 3 of Applicants' invention. In fact, the Examiner notes that SEQ ID NO: 43 differs from nb 430-445 of SEQ ID NO: 3 of Applicants' invention by 1 nucleobase.

Baker does not teach or suggest antisense oligonucleotides, specifically those 12 to 30 nucleobases in length, targeted and 100% complementary to a nucleic acid molecule encoding human apo(a) (SEQ ID NO: 3). Nor

PAGE 8/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26

does Baker teach or suggest antisense oligonucleotides 12 to 30 nucleobases in length targeted and 100% complementary to at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding human apo(a) (SEQ ID NO: 3) as taught by pending amended claim 11 of Applicants' invention.

In view thereof, the sequences of Baker are not targeted and 100% complementary to the nucleic acid molecule encoding SEQ ID NO: 3, as required by the pending claims of Applicants' invention. Thus, Baker cannot properly be applied as an anticipation reference.

Reconsideration and withdrawal of this rejection are requested.

(iii) *Claims 1, 2, 11, 12, and 14 are rejected under 35 USC § 102(b) over McLean et al., Nature, 330:132-137 (1987).*

The Examiner asserted that the synthetic 30-base oligonucleotide in Figure 1b under the dotted underlining is reverse complementary to nb 80-109 of SEQ ID NO:3 of Applicants' invention.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

Claims 2 and 14 is canceled, thereby mooting the outstanding rejection as applied to these claims. Further, claim 1 is amended by incorporating the subject matter of claims 4, 6, and 8, which are not subject to this rejection. In view of these amendments, this rejection is moot as applied to claims 1 and 12.

PAGE 9/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26

Claim 11 is therefore subject to this rejection and has been amended herein to incorporate the modifications discussed in claims 4, 6, and 8.

McLean discusses the sequence of cloned human Apo(a) cDNA, and demonstrates that various segments of the Apo(a) sequence show between 78% to 100% sequence homology to plasminogen. McLean discusses a 30-nb oligonucleotide (Figure 1b, dotted underline) probe that is reverse complementary and contiguous to nb 80-109 of SEQ ID NO: 3 of Applicants' invention. McLean however does not discuss modifying the probe discussed therein or using the probe for any other purposes other than sequence identification.

The pending and amended claims of Applicants' invention require that the antisense oligonucleotide have at least one modification selected from a modified internucleoside linkage, modified sugar moiety, or modified nucleobase. Thus, McLean cannot properly be applied as an anticipation reference.

Reconsideration and withdrawal of this rejection are requested.

35 USC § 103 Rejection

Claims 1, 2, and 4-15 are rejected under 35 USC § 103(a) over McLean, in view of Morishita (Circulation, 98:1898-1904, 1998) and Baracchini et al. (US Patent No. 5,801,154) and McKay et al. (US Patent No. 6,258,601).

In this present rejection, the Examiner asserted that it would have been obvious to:

1. *Make an antisense oligonucleotide compounds targeted to a nucleic acid encoding Apo (a)(i) using the nucleic acid Apo (a) sequence of*

McLean, (ii) the motivation of Morishita which generally teaches making inhibitors to Apo (a) using ribozyme nucleic acids, (iii) the knowledge in the art which assertedly teaches that antisense oligonucleotides and ribozymes are art-recognized functional equivalents, and (iv) the section in the instant specification (page 11, line 35) that recites "Antisense compounds include ribozymes";

2. *Make an antisense oligonucleotide having a length within the range of 12-30 nucleotides, having a modification as taught by Baracchini and delivering the same in combination with a carrier, all as assertedly taught by Baracchini; and*

3. *Use antisense compounds targeted to a nucleic acid encoding Apo (a) for inhibiting expression of Apo (a) in cells in vitro since Morishita suggests that ribozymes targeted to Apo (a) inhibit expression of Apo (a) in cells in vitro.*

Claims 2, 4, 6, 8, and 14 are canceled, thereby mooting the outstanding rejection as applied to these claims. Claims 1, 5, 7, 9-13, and 15 are therefore subject to this rejection.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons. McLean in combination with the generic secondary references does not suggest the desirability of the invention of Applicants' amended claims, as required to make an obviousness rejection. See, MPEP §2143.01.

The combination of McLean's disclosure of the known sequence of Apo (a) with Morishita's 42-mer ribozymes and the general teachings of Baracchini and McKay does not suggest the modified 12 to 30 nucleobase antisense

PAGE 11/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26

sequences of the amended claims of the present invention and uses thereof. Specifically, no combination of the probe of McLean with the secondary references suggests the modified antisense compounds of the present invention that are targeted and 100% complementary to a nucleic acid molecule encoding Apo (a). In fact, the combination of McLean and Morishita with the remaining secondary references cannot be made in view of the negative teachings of Morishita with regard to antisense sequences as discussed in Response filed on August 9, 2004 and briefly below.

As the Examiner is aware, Morishita is directed only to ribozymes and to a DNA oligonucleotide that are each about 42 nucleobases in length. As previously discussed, even minimal ribozymes require about 40 nucleotides in length to properly operate. Morishita is therefore an ineffective reference for use in this obviousness rejection because not only do its compounds fail to meet all structural requirements of the amended claims, but Morishita teaches away from the antisense sequences of Applicants' amended claims.

One of skill in the art would also readily recognize that Applicants' statement on page 11 ("...antisense compounds include ribozymes...") would not include antisense compounds that are less than 40 nb in length, such as those provided by Morishita.

Therefore, the combination of the primary McLean reference, which only provides a reference to a probe corresponding to the publicly available sequence of Apo(a), which probe ***does not*** meet the modification requirements of

amended claims 1 or 11 of Applicants' invention, the Morishita secondary reference which teaches away from Applicants' invention, and the remaining secondary references do not provide a motivation for one to prepare the antisense compounds of Applicants' claims 1 and 11.

Further, Baracchini and McKay cannot be combined with McLean and Morishita since these secondary references refer to targets that are completely unrelated to Apo(a), i.e., Baracchini refers to antisense compounds that hybridize with a nucleic acid encoding multidrug resistance-associated protein (MRP) and McKay refers to antisense oligonucleotide compounds which specifically hybridize with a nucleic acid sequence encoding Jun N-terminal kinase (JNK). McKay's probe is used only for the identification of sequences and is not asserted to have any other utility. There is nothing in Baracchini or McKay to assist in overcoming the negative teaching in Morishita about the use of antisense strategies applied to Apo(a).

Therefore, Applicants respectfully submit that this combination would not have motivated one of skill in the art to make or modify McLean's compounds to meet the requirements of Applicants' amended claims. In fact, the person of skill in the art might draw the opposite conclusion based on the teachings of Morishita. The motivation to make the sequences claimed by Applicants' is derived from Applicants' disclosure only. Applicants' disclosure cannot be used as the source for such motivation to make an obviousness rejection.

Reconsideration and withdrawal of this rejection are requested.

PAGE 13/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26

DOCKET NO.: ISPH-0595 PATENT

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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PAGE 14/14 * RCVD AT 2/1/2005 2:49:54 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/0 * DNIS:8729306 * CSID:2155405818 * DURATION (mm-ss):03-26